REMARKS

This application is amended in a manner to place it in condition for allowance at the time of the next Official Action.

Status of the Claims

Claims 1-18 and 21-32 have been amended.

Claim 1 has been amended substantively. Support may be found as follows:

- at least one liquid excipient: claim 1;
- extended release composition: original claims 9 and 12 and lines 8-12 from the bottom page 3;
- a pressurised aerosol: claim 2;
- non-pressurised aerosol: claim 24; Page 15 and 16, i.e., in that the expression "non-pressurised aerosol" are "liquid sprays";
- a mixture of water and a pressured aerosol propellant: claim 2 and 3, and selected from dimethylether, butane, propane, mixtures of butane and propane, fluorinated hydro carbons, nitrogen, carbon dioxide and nitrous oxide: claim 2;
- mixtures of water and butane; claim 2, 3 and 4;
- fluorinated hydro carbons or propane: claim 2;

- when the preparation is in the form of a non-pressurised aerosol is water or a mixture of water and an organic solvent: claim 4;
- at least one solid excipient which essentially is insoluble in the liquid excipient: claim 1;
- after actuation of the spray suspension forms a matrix into which at least one pharmaceutical active ingredient is incorporated: claim 1, claim 8, paragraph bridging pages 6 and 7 especially page 7 lines 2-5.

Claims 2-4 have been amended to correspond to amended claim 1, and claims 5-18 and 21-32 are amended as to form, e.g., to recite the features in a definite manner.

Claims 1-32 remain in this application.

Claims 14 and 19-20 have been withdrawn.

Claim Rejections-35 USC §112

Claims 3, 7, 11, 15 and 17 were rejected under 35 U.S.C. §112, second paragraph, for being indefinite. This rejection is respectfully traversed for the reasons that follow.

Claim 3 now only recites the broad range.

Claim 7 refers to milled micro crystalline cellulose. That is, claim 7 refers to even more fine-particulate than those commercially available. In Example 1, Avicel® Ph105 (a commercial quality of microcrystalline cellulose) is used. A skilled person would appreciate that microcrystalline cellulose refers to

commercially available microcrystalline cellulose, which normally exist in powder form (i.e. particulate form), such as Avicel® Ph 105. Thus, it is believed to be readily understood that claim 7 refers to very fine microcrystalline cellulose, i.e., even finer that that which is commercially available.

As to claim 11, the parentheses have been removed.

Regarding claims 15 and 17, the narrow languages has been removed, and claim 1 has been amended to provide support for the "porous suspension" recited in claim 17.

Therefore, the claims are now believed to be definite, and withdrawal of the rejection is respectfully requested.

Claim Rejections–35 USC §102 and 35 USC §103

Claims 1-5, 8-12, 16, 22 and 25 were rejected under 35 U.S.C. §102(b) as being anticipated by US 4,450,151 ('151').

Claims 15, 21, 24 and 26-32 were rejected under 35 U.S.C. §103(a) as being unpatentable over '151'.

These rejections based on '151 alone are respectfully traversed for the reasons below based on three significant differences.

A. Composition and Preparations

The Claimed Invention

As described both in the description and in the claims, the composition may be used for two principal spraying devices:

pressurised aerosol or a mechanical pump device (e.g., claim 24). These two devices require different liquid excipients for dispersing the pharmaceutical active ingredient and the solid, insoluble excipient (i.e. the solid excipient suspended in the liquid). Thus, two sets of compositions are described in the present set of claims.

Claims 1-3: When a pressurized aerosol is used, the liquid of the composition is a pressured aerosol propellant, such as dimethylether (claim 2), but could preferable include water (claim 3). A propellant is under ambient condition a gas, but in the pressurized device it exists in liquid form. Thus, here the solid excipient is suspended in the propellant or in the mixture of propellant and water.

Claims 1 and 4: When a mechanical pump device is used, the liquid of the composition is water or a mixture of water and an organic solvent, such as alcohols (claim 4). Thus, here the solid excipient is suspended in water or the mixture of water and an organic solvent.

US 4,450,151 (‘151’)

In the cited ‘151’ document a composition for a pressurized aerosol is described. Thus, here a propellant is a compulsory part of the composition. This is in contrast to the suggestion made in the Official Action, which indicates that the addition of the propellant is only needed to prevent clogging induced by the presence of a hydrophobic component.

Instead, however, '151' teaches that when hydrophobic solid substances are part of the composition, the portion of hydrophobic substance must be lower than 10 wt % and the proportion of the propellant must be higher than 80 wt %. Thus, the propellant is always a part of a pressurized aerosol composition, but the proportion needed is higher when hydrophobic components are added.

This is also the problem that is addressed in '151', namely how to obtain a functioning composition using a hydrophobic component, suspended in water and alcohol and how at the same time keep the proportion of propellant to a maximum of 40 wt%. How '151' has solved this problem is unclear, but it is obvious that what is described in '151' is a composition that is different from the composition of the claimed invention for at least the following reasons:

1. The Liquid Excipients

In '151' the composition contains the following liquid components: propellant, water and alcohol. In the present invention, the composition for pressurized aerosol (claims 1-3) contains propellant or propellant and water. No alcohol is used in the pressurized aerosol composition according to the now limited claim 1. The use of alcohol might be needed in '151' due to the hydrophobic addition, which in turn is used for the intended use as antiperspirant, water-eczema remedy, dry shampoo, baby powder etc. In the present invention no such additions are

needed or wanted since the invention is directed towards quite another application – the formation of a retarded release matrix formulation.

2. The Solid Excipient Particles

In '151' the addition of solid excipient particles are limited to hydrophobic materials. In the present invention only hydrophilic components are mentioned, such as microcrystalline cellulose. It is respectfully noted that a material does not have to be hydrophobic in order to be suspended, i.e., a material does not have to be hydrophobic to possess a low solubility in a liquid such as water. Many hydrophilic materials such as calcium carbonate, barium sulphate, etc are practically insoluble in water. This is also the case for the excipient materials used in the present invention, they are hydrophilic but could still be used for the preparation of suspensions.

3. The Suspension of the Particles

In '151' the hydrophobic particles are suspended in a mixture of water and alcohol, whereafter this suspension "is placed in an aerosol container along with a propellant such as liquefied petroleum gas or dimethyl ether which is lower in specific gravity than the suspension". It is also expressed in claim 1 that "the resulting suspension having a pH in the range of 5 to 9 and a viscosity in the range of 50 to100 cps". From the description it is clear that this suspension only refers to a

liquid phase consisting of water and alcohol, and does not include the propellant.

In the present invention as now defined in the amended claim 1, the solid excipient particles are suspended in the propellant or a mixture of the propellant and water. Thus, in the present invention the propellant does not exist as a separate phase in the aerosol container.

4. The Matrix Holding the Active

In the present invention the composition will form a matrix for retarded drug release. '151' is totally silent in this respect.

B. Particle Size of Excipient Material

Regarding particle sizes of the excipient material in the present invention, two different classes are described.

1. Fine-Particulate Quality

That is, the first class of particles is one having at least 90 % by weight of the particles are smaller than 50 µm (claim 10). In Example 1, Avicel® Ph105 (a commercial quality of microcrystalline cellulose) is used. According to the manufacturer's product specification, practically no particles are larger than 38µm. This part of the invention thus deals with the use of very small primary particles of the excipient material, capable of forming a matrix *in situ* on the skin, i.e.

forming a multilayer of excipient particles wherein the active ingredient is incorporated.

In ‘151’ the hydrophobic particles are claimed to have an average particle size between 325 to 70 mesh, i.e., between 44 to 210 µm, which is a size larger than what is claimed, regarding the first class of excipient particle fineness.

2. Larger Composite Particles

That is, the second class of particles include at least 50 % by weight of particles are larger than 10µm and at least 90 % by weight of the particles are smaller than 150µm (claim 15). Such particles are prepared in Example 2 of the present patent application. This part of the invention thus deals with the use of preformed, larger secondary particles prepared e.g. by spray-drying before being suspended in the liquid. Such particles must obviously be pre-formed in order to be coherent enough and especially to incorporate the active ingredient in a homogenous manner. Further, in order to avoid clogging in the valve of the spray device, the particle shape must be as spherical and smooth as possible (claim 16).

The Official Action notes that “the very reason to include gas propellant is to prevent clogging by aggregates. Thus it is implicit that the powder particles of ‘151’ form large aggregates as in claim 12." This conclusion, however, is not correct. The fact that hydrophobic materials sometimes have a tendency to form larger aggregates within an aqueous surrounding

does not teach the use of preformed, composite particles, based on hydrophilic excipient materials where the drug is incorporated into the pore structure, or matrix, of these secondary, excipient particles. To avoid any misunderstanding it must be mentioned that a secondary particle normally is defined as a larger aggregate of smaller primary particles. In the present patent application such particles into which the active ingredient is incorporated are denoted "suspension particles". The limited claim 1 now defines that the active ingredient is incorporated into the matrix formed after spraying.

C. Particle Shape Of Large Excipient

Regarding the particle shape of the larger “suspension particles” of the present invention, ‘151’ fails to teach that a spherical shape and smooth surface is preferred. The disclosure that “powder particles do not fly and adhere to the skin uniformly” gives no indication in this context.

Instead, this may suggest the contrary. In order to adhere to the skin an irregular particle shape would be preferred. Further, the materials mentioned in ‘151’, such as talc and kaolin are known to be fine-particulate and with flaky particle shape, i.e. far from large, isodiametrical particles.

Therefore, in view of the above, ‘151’ alone neither anticipates nor renders obvious claims 1-5, 8-12, 15, 16, 21, 22, and 24-32.

Claims 17-18 were rejected under 35 U.S.C. §103(a) as being unpatentable over '151', further in view of GORDON US 6,001,336 (GORDON). This rejection is respectfully traversed for the reasons that follow.

'151' fails to disclose or suggest the claimed invention according to claims 1 and 11 (the claims from which claims 17 and 18 depend) for the reasons discussed above.

GORDON fails remedy the shortcomings of '151' for reference purposes.

In GORDON, a spray-drying method for preparing very small particles (less than 10 µm) of hydrophobic drugs is described. This is in contrast to the present invention where larger aggregate particles (denoted "suspension particles" in the present patent application) are described. In order to obtain almost spherical aggregate particles it was found that an initial milling, i.e. size reduction of either the mixture of excipient and drug particles or just excipient particles (claims 17 and 18) was advantageous. If these porous particles formed do not contain an active ingredient, the subsequent intrusion of the active ingredient is necessary (claim 18). Thus, there is no suggestion in GORDON that in order to obtain larger, isodiametrical aggregate particles, one should use of the method described in claims 17 and 18.

Instead, GORDON teaches that milling and spray-drying could be used to obtain very small particles of hydrophobic drugs, provided that the drug particles are suspended in a water solution of a hydrophilic excipient, prior to spray-drying.

Therefore, the combination of '151' and GORDON fails teach or suggest the method of claims 17 and 18, and withdrawal of the rejection is respectfully requested.

Claims 6 and 7 were rejected under 35 U.S.C. §103(a) as being unpatentable over '151', further in view of HALSWANTER et al. US 6,841,146 ('146'). This rejection is respectfully traversed for the reasons below.

'151' fails to disclose or suggest the claimed invention according to claim 1 (from which claims 6 and 7 depend) for the reasons discussed above.

'146' fails to remedy the shortcomings of '151' for reference purposes.

'146' discloses a spray composition for a mechanical pump device. Thus, the composition is based on a water solution of the pharmaceutical active ingredient.

In order to increase the retention time in, e.g. the nasal cavity, and allow the fluid composition to be administered from the pump device, a gel forming additive is also included in the composition. This gel-forming additive is both in claim 1 and in the description denoted either as Avicel™ RC-591 (alternatively Avicel™ RC-581) or in the more chemical terms as a

spray-dried blend of microcrystalline cellulose and an alkali metalcarboxyalkylcellulose.

This additive is totally different from the claimed microcrystalline cellulose. While, microcrystalline cellulose, i.e., pure microcrystalline cellulose, is inert and will not react with water, the cellulose mixture used in '146' will partly dissolve and form a thixotropic gel. The gel-structure (i.e. a three-dimensional continuous network in the water-phase) will correspond to an increased viscosity when the composition is at rest. This also the aim of the '146' invention - to obtain a prolonged residence time for the composition after administration, e.g., to the nasal mucosa. This achieved by the increase in viscosity due to the gel-forming additive. At the same time, due to the thixotropic nature of the gel, the composition will during actuation from the pump device possess a much lower viscosity, due to the applied shear forces. In claim 1 of '146', it is clearly expressed that the addition of the excipient will induce thixotropic properties to the water composition. That is the excipient is a gel-forming excipient far from pure microcrystalline cellulose which is inert and water-insoluble.

In the present invention, a composition intended for a mechanical pump device is disclosed in claim 1 in combination with claim 4. Here water or a mixture of water is used as the liquid phase. But in contrast to '146', the solid excipient that

is added must be insoluble in the liquid to form a suspension. In '146', no suspension is formed. The use of the cellulose based additive in '146' will instead result in a thixotropic gel. The gel-forming constituent can by definition never form a suspension, i.e. form discrete particles surround by the homogenous, liquid phase. The added cellulose material in '146' forms a continuous, homogenous network.

Thus, for several reasons it would not have been obvious to include microcrystalline cellulose from '146' to the composition of '151', as

1. Microcrystalline cellulose in its pure form is not used in '146'.

2. Microcrystalline cellulose is not a hydrophobic material.

3. The cellulose material used in '146' is partly dissolved in water and forms a gel, and thus not represents the type of excipient material described in the present invention.

4. '146' deals with a mechanical pump device, while '151' describes a pressurized aerosol.

Therefore, the proposed combination failed to render obvious claims 6 and 7, and withdrawal of the rejection is respectfully requested.

Claims were rejected under 35 U.S.C. §103(a) as being unpatentable over . This rejection is respectfully traversed for the reasons below.

Therefore, withdrawal of the rejection is respectfully requested.

Conclusion

In view of the amendment to the claims and the foregoing remarks, this application is in condition for allowance at the time of the next Official Action. Allowance and passage to issue on that basis is respectfully requested.

Should there be any matters that need to be resolved in the present application, the Examiner is respectfully requested to contact the undersigned at the telephone number listed below.

The Commissioner is hereby authorized in this, concurrent, and future submissions, to charge any deficiency or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

YOUNG & THOMPSON

/Robert A. Madsen/

Robert A. Madsen, Reg. No. 58,543
209 Madison Street, Suite 500
Alexandria, VA 22314
Telephone (703) 521-2297
Telefax (703) 685-0573
(703) 979-4709

RAM/jr